JAPANESE [JP,05-004925,A]

CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART TECHNICAL PROBLEM MEANS EXAMPLE

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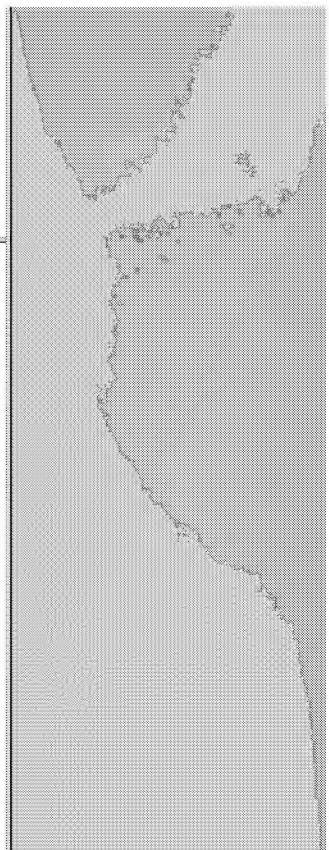


* NOTICES *

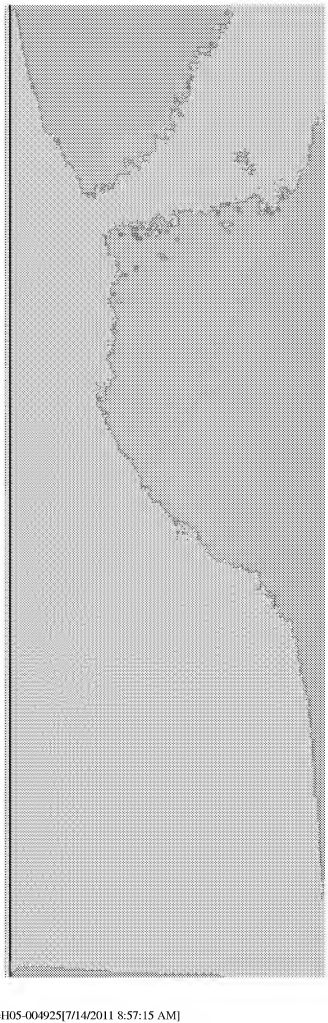
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application]This invention relates to alfacalcidol soft capsule pharmaceutical preparation suitable for improving preservation stability of alfacalcidol.
[0002]
[Description of the Prior Art]Although alfacalcidol is a compound which participates in the metabolic turnover of calcium as a homologous compound of vitamin D_3, and physiology activity is strong and is used for Medical Science Division rather than vitamin D_3, Since it is that it is easy to change in response to the influence of light and oxygen, that it is oil solubility, and also a thing that demonstrates an effect by the very small amount used mug, various devices are made by pharmaceutical preparation-ization.
[0003]For example, the method of encapsulating using the husks containing the oily base which took and removed dissolved oxygen, and the optical absorption agent which absorbs the light of a specified wavelength in order to add a reducing substance and to lose the influence by the others and light which it is using an oily base etc. is taken. Since the oily base currently used in here is what is called vegetable oil of natural origin, although it hydrogenates and the degree of saturation is raised, it is difficult to saturation-ize the unsaturation fatty acid part contained thoroughly, for example, judge the degree of unsaturation of ingredient slack fatty acid with iodine value, but. It is fractionation coconut oil which has raised refining, and the index is 5.
[0004]Thus, the unsaturated ingredient was removed, or the reducing

substance was added, and stabilization of alfacalcidol which is the main ingredients is measured. Completeness is not expectable as long as removal of a degree of unsaturation also uses vegetable oil.
[0005]Since it is such, in order to improve storage stability of a pharmaceutical preparation article further, it is in the actual condition that various devices are performed. However, it is desired for using addition of a reducing substance abundantly on the character of a thing to stop undesirably to the minimum. The tar dye used for optical absorption also has the operation which is not preferred to the living body, and also makes the appearance of a pharmaceutical preparation article not so good for the coloring which is not preferred.

[0006]
[Problem to be solved by the invention]This invention protects alfacalcidol from changing over a long period of time, and provides storage stability with the soft capsule pharmaceutical preparation of ** alfacalcidol immediately.
[0007]
[Means for solving problem]The soft capsule of alfacalcidol excellent in the storage stability provided by this invention is built as follows.
[0008]That is, since alfacalcidol is oil solubility, fatty acid triglyceride is used for a carrier, but the fatty acid glycerol ester used as a carrier is good to choose what does not contain unsaturated fatty acid. The iodine value which is an index of a degree of unsaturation is one or less thing, and the JSPI medium-chain-fatty-acid triglyceride (only henceforth medium-chain-fatty-acid triglyceride) currently chemically manufactured as what fulfills this condition is raised.
[0009]Since alfacalcidol has a hydroxyl group and a double bond in intramolecular, and it is easy to receive oxidation, it is a best policy to use an anti-oxidant, but. This invention persons found out variously that it was effective to use dibutylhydroxytoluene (it is written as BHT) and dl-**-tocopherol at a rate of the weight ratio 1:1 as a result of examination.
[0010]Alfacalcidol, and BHT and dl-**-tocopherol hit to medium-chain-fatty-acid triglyceride selected as optimal carrier at a rate of 1:1 by a weight ratio, and it adjusts as contained at least 0.005% by gross weight.
[0011]Although an anti-oxidant of BHT or dl-**-tocopherol is very effective when it improves alfacalcidol storage stability, It is not preferred to use it abundantly at that which may have on a metabolic turnover (for example, there is a report that it is tocopherol 100 mg/dayx19weeks administration and phosphate metabolism of a rat was anti-**(ed)). It is good for both persons to double in this invention, even if large, and to limit to 0.03%.
[0012]In this invention, first, alfacalcidol is melted in dl-**-tocopherol, a small amount of medium-chain-fatty-acid triglyceride is added to this, and it mixes with medium-chain-fatty-acid triglyceride of an appropriate after large quantity, and let the preparation procedures of a drug solution for accommodating in a capsule be homogeneous solutions.
[0013]In this way, the medium-chain-fatty-acid triglyceride solution of preparation **** alfacalcidol is stored in the gelatine capsule husks containing titanium oxide and glycerin. The place where



gelatin husks are built with titanium oxide, glycerin, and gelatin, titanium oxide is added 1.5 to 35% to gelatin in the thing of the particle size distribution centering on the particle diameter of 0.2-0.5 micrometer, and that to which glycerin was added 20 to 25% to gelatin is used.

[0014]In this way, the alfacalcidol soft capsule pharmaceutical preparation provided by this invention became clear [excelling in storage stability].

[0015]An working example is shown below and the effect of this invention is described concretely.

[0016]

[Working example]

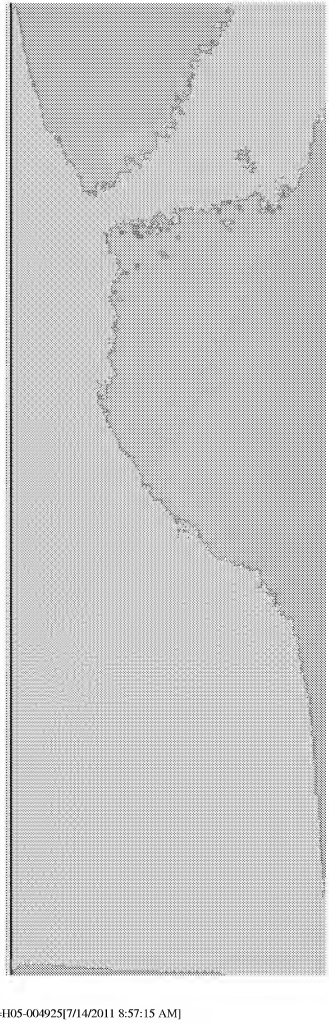
About that in which prescribes example 1 alfacalcidol, dl-**-tocopherol, and BHT so that it may become a content given in a table 1 formula column, and dl-**-tocopherol is contained. First, alfacalcidol was melted in dl-**-tocopherol and this was mixed with medium-chain-fatty-acid triglyceride or medium-chain-fatty-acid triglyceride containing BTH. If it was in the formula of those other than this, alfacalcidol was adjusted using the adequate amount of medium-chain-fatty-acid triglyceride containing BHT, using optimum dose of medium-chain-fatty-acid triglyceride so that it might become a predetermined content. The total amount of the prepared solution was 1000 g per each formula.

[0017]In this way, a prepared drug solution was covered with content **** gelatin film by having made titanium oxide into a shielding agent, and was used as an alfacalcidol soft capsule. A drug solution content in 1 capsule was 100 mg. About what neglected a soft capsule by a release position to a room temperature (temperature of 3-30 **, 26 to 70% of relative humidity), storage stability measured a content of chief remedy alfacalcidol, and measured it with it of a soft capsule immediately after manufacture. The measuring method is as follows. Quantity of a chief remedy takes a capsule of a number corresponding to 20microg, takes out contents, and weighs quantity of contents precisely. After adding 4 ml of internal standard solutions correctly, dichloromethane methanol mixture (50:1) is added to make exactly 20 ml, and it is considered as a standard solution. About 0.1 mg of alfacalcidol reference standards are measured precisely independently, and it dissolves in dichloromethane methanol mixture (50:1) to make correctly 20 ml. After measuring 4 ml of this liquid correctly and adding 4 ml of internal standard solutions correctly, dichloromethane methanol mixture (50:1) is added to make exactly 20 ml, and it is considered as a standard solution. About sample-solution and standard solution 100mul, it examines by liquid chromatography on the following conditions, and the ratios Qt and Qs of a peak area of alfacalcidol to that of an internal standard substance are calculated.

アルファカルシドール（$C_{27}H_{44}O_2$）の量（μg）

$$= \text{アルファカルシドール標準品の量（μg）} \times \frac{Qt}{Qs} \times \frac{1}{5}$$

An internal standard solution Dichloromethane methanol mixture (50:1) is added to 0.01 g of chlorphenesin carbamate, and it melts,



and may be 100 ml.
An operating-condition detector: An ultraviolet-rays absorptiometer (a measured wavelength: 265 nm)
A column: Fill up a stainless steel tube about 4 mm in inside diameter, and about 25 cm in length with 5-micrometer silica gel.
column temperature: -- constant temperature mobile phase [near 50 **]: -- dichloromethane methanol mixture (50:1)
A flow: Adjust so that retention time of alfacalcidol may become about 10 minutes.
Selection of a column: When operating it under the above conditions about standard solution 100mul, elute alfacalcidol and an internal standard substance in this order, and the degree in separation uses 2.0 or more things.
When quantified by alfacalcidol which passed as a raw material of a reference standard, a reagent, and test solution (1) reference-standard alfacalcidol reference standard pharmaceutical preparation, it is a thing beyond alfacalcidol ($C_{27}H_{44}O_2$) 99.9%.
(2) What suits a reagent and test solution chlorphenesin carbamate JSPI chlorphenesin carbamate ($C_{10}H_{12}ClNO_4$).
Chief remedy alfacalcidol content change of each formula was as given in a table 1 measurement result column. About a measurement result, it was referred to as 100, and measured value of a thing immediately after manufacture was relengthened, and was displayed.
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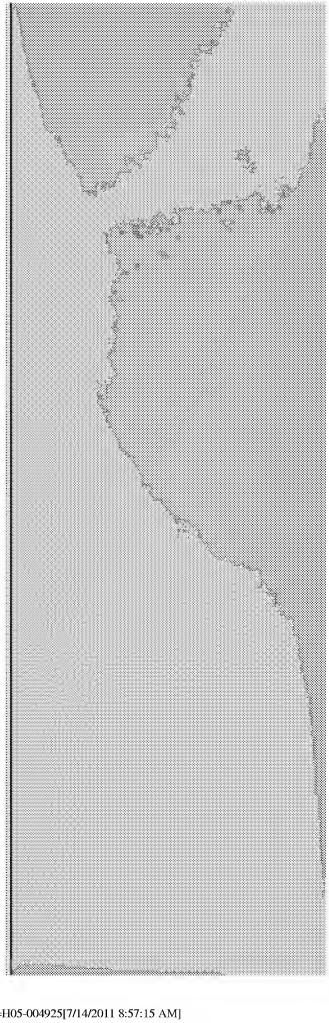

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